REMARKS

Claims 16-22 and 25-28 are pending in this application. By this amendment, applicants have amended claim 16 to better recite applicant's invention. Support for the amendment to claim 16 may be found in the specification which states that the invention relates to the use of DHA "as active substance". Applicants note that "as active substance" is akin to "as the only active substance". In plain English, the use of an article such as "a" or "an" would denote that there may be possibilities of different substances. When no such article is used, the connotation is that the substance is unique or stand alone. So that if the specification stated that DHA is used as "an active substance", one could understand that there may be other active substances. However, the specification indicates that DHA is used "as active substance", i.e. as the active substance. In addition, there is no other potential substance disclosed in the application which is suggested to be another active substance. Accordingly, applicants respectfully request that the Examiner enter and consider this amendment as it is supported by the original disclosure.

Rejection Under 35 USC § 102

The Examiner rejected claims 16-22 and 25-28 under 35 U.S.C. 102(e) as anticipated by Pacioretty and Babish, U.S. Application Publication No. 2004/0106591.

In response, in addition to the arguments set forth in the paper filed on June 25, 2010 in connection with the subject application, applicants note that in the July 6, 2010 Advisory Action, the Examiner indicates that the amendment made to claim 16 if entered would overcome this rejection. Applicants maintain that the amendment should be entered and as discussed above is supported by the specification. Accordingly, this rejection should be reconsidered and withdrawn.

Rejection Under 35 USC § 103

The Examiner maintained the rejection of claims 16-22 and 25-28 under 35 U.S.C. 103(a) as unpatentable over Holstein et al. in view of Connor et al. and stated that even if the amendments herein were entered, the rejection would stand. In making this rejection, the Examiner indicates that hyperlipidemia can be considered as a form of lipodystrophy. Applicant respectfully

traverses this ground of rejection and insists on the difference between hyperlipidemia and lipodystrophy.

Applicants again disagree with the Examiner's assessment. Lipodystrophy is defined in the subject application paragraph 0007 and 0008 of the published applicaction as follows:

> *"Briefly, the patients show loss of fat in the face, buttocks, extremities and thorax, accompanied by accumulation of fat inside the abdomen, the back of the neck and in the breast area in women, together with increase plasmatic levels of cholesterol, triglycerides, lowering of HDL cholesterol (protective cholesterol) and increase of LDL cholesterol (harmful cholesterol), insulin resistance (occasionally diabetes) and occasionally arterial hypertension. This entire set of situations is known as lipodystrophy syndrome.".*

Therefore, lipodystrophy in patients who are receiving a HAART treatment is not merely an alteration in the body-fat distribution but an illness with multiple associated factors involving the metabolism of fatty acids and the metabolism of carbohydrates.

Applicant hereby submits additional evidence to show that treating one of the main symptoms of lipodystrophy is NOT the same as treating lipodystrophy, and that shows that hyperlipidemia and lipodystrophy do NOT have the same patient population.

Applicant submits herewith a copy of Petersen et al, **Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy,** *Journal of Clinical Investigation* (2002), 109(10), 1345-1350, which shows that lipodystrophy is not only comprised of symptoms related to fat disorder but also to carbohydrates, e.g. glucose or insulin.

> *Lipodystrophy is a rare disorder that is characterized by selective loss of s.c. and visceral fat and is assocd. with hypertriglyceridemia, hepatomegaly, and disordered glucose metab. It has recently been shown that chronic leptin treatment ameliorates these abnormalities. Here we show that chronic leptin treatment improves insulin-stimulated hepatic and peripheral glucose metab. in severely insulin-resistant lipodystrophic patients. This improvement in insulin action was assocd. with a marked redn. in hepatic and muscle triglyceride content. These data suggest that leptin may represent an important new therapy to reverse the severe hepatic and muscle insulin resistance and assocd. hepatic steatosis in patients with lipodystrophy.* Abstract (Emphasis Added)

Applicants maintain that a drug useful for one of the symptoms of lipodystrophy does not necessarily indicate that such drug will be also useful for the treatment of the disease lipodystrophy itself. As evidence, applicants submits a copy of Sheth et al., **The Efficacy and Safety of Insulin-Sensitizing Drugs in HIV-Associated Lipodystrophy Syndrome: A Meta-Analysis of Randomized Trials,** *BMC Infectious Diseases (2010)*, 10:183. This publication shows that lipodystrophy in patients who are receiving a HAART treatment is more than an alteration in the body-fat distribution. See for example the Abstarct which states in relevant part that "HIV-associated lipodystrophy syndrome (HALS) is characterized by insulin resistance, abnormal lipid metabolism and redistribution of body fat" (Emphasis Added).

Applicants maintain that because lipodystrophy is characterized by an insulin resistance, the authors of the publication inquired about the possibility of using the same drugs for improving insulin sensitivity (rosiglitazone, pioglitazone and metformin) in patients suffering from lipodistrophy who are receiving a HAART treatment. However, these assumption proved to be incorrect. The results show that only metformin had any beneficial effects, and that rosiglitazone should even be considered as a non-advisable drug for treatment. Accordingly, along parallel lines of reasoning, one cannot confirm that drugs for treating specific hyperlipidemia can also be useful for treating lipodystrophy since there is carbohydrate metabolism involved. As shown the Macallan et al. publication, it could even be non advisable to generalize the use of a drug for treating "related" diseases.

Applicant also submits a copy of Macallan et al., **Treatment of Altered Body Composition in HIV-Associated Lipodystrophy: Comparison of Rosiglitazone, Pravastin, and Recombinant Human Growth Hormone**, *HIV Clin Trials 2008, 9(4):254-268.*

The conclusion reached by Macallan et al. is similar to that of Sheth et al. above. That is that none of the drugs used for specific conditions related to the symptoms of lipodystrophy can be generalized with short- and long-term benefits as a drug for treating lipodystrophy itself in a patient with HIV under a treatment with HAART. It is also showm that a statin like pravastatin is not optimal for the treatment of lipodystrophy, but is for treating hypercholesterolaemia. Finally, it is disclosed that complementing drugs like rosiglitazone and pravastatin, which are indicated to treat insulin resistance and hypercholesterolaemia, respectively, and which are two of the symptoms of lipodystrophy, have negative interaction between them. Accordingly, this demonstrates that it is not follow that a drug used to treat symptons common to diseases will also

treat the disease itself especially in a patient with HIV under a treatment with HAART. This is a specific finding which the present inventors has achieved.

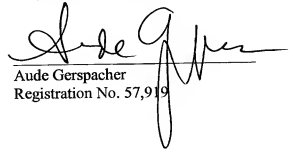
Applicants further maintain that one skilled in the art at the time of filing the subject application would not have made such an assumption regarding the treatment of symptoms of lipodystrophy and the treatment of lipodystrophy itself. As evidence, applicants submit herewith a copy of Sutinen et al., **Rosiglitazone in the Treatment of HAART-Associated Lipodystrophy – A Randomized Double-Blind Placebo-Controlled Study** (2003) *Antiviral therapy* 8:199-207.

In Sutinen et al.,the last sentence of the Abstract on page 199 states that "Rosiglitazone unexpectedly caused significant increases in serum triglyceride and cholesterol concentrations". In addition on page 205, Sutinen et al. state the following: "In conclusion, rosiglitazone had several unexpected effects in patients with HIV lipodystrophy syndrome. These data imply that rosiglitazone is unlikely to reverse HIV lipodystrophy syndrome with ongoing antiretro-viral therapy." Applicants maintains that this demonstrates that using drugs for treating one of the symptoms of lipodystrophy does not translate to the drug also being useful for treating the disease lipodystrophy as a whole with all the symptoms associated. Rosiglitazone is known as a insulin-sensitizing anti-diabetic agent. Because lipodystrophy has as one of its symptoms insulin resistance, it was thought that a drug already used for that symptom alone could be useful. As shown by Sutinen et al., there exists the need of a unique drug useful for treating all symptoms associated with lipodystrophy. Again, the present invention provides that solution.

Accodingly, applicants maintain that the claims are not rendered obvious over Holstein et al. in view of Connor et al. Connor et al. do not cure the deficiencies of Holstein et al. Connor et al. teach the effect of dietary n-3 fatty acids from fish and fish oil in hypertriglyceridemic patients with combined hyperlipidemia (See Abstract). Being hyperlipidemia alone, or hypertriglyceridemia combined with hyperlipidemia, two clinical conditions different from lipodystrophy, there is no suggestion in Connor et al. that dietary n-3 fatty acids could be as well effective in lipodystrophy. And as such, there are yet no drugs currently approved for the treatment of lipodystrophy. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Reconsideration and allowance of all the claims herein are respectfully requested.

Respectfully submitted,



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Aude Gerspacher
Registration No. 57,919

Cozen O'Connor
250 Park Avenue
New York, New York 10177-0030
Telephone: 212.986.1116